REMARKS

Withdrawal of Rejections

Applicant thanks the Examiner for careful consideration of Applicant's amendments and arguments filed on March 21, 2005, and the withdrawal of the rejections under 35 U.S.C. § 103 and 35 U.S.C. § 103 based on the applied references.

Finality of Office Action

In response to the Final Office Action, Applicant respectfully requests that the Examiner enter the foregoing amendments and consider the following remarks because the claims have been placed in condition for allowance. In the alternative, Applicant requests that the claims amendments be entered because they better place the claims in condition for an appeal.

Claim Rejections under 35 U.S.C. § 103

(a) Claims 1, 7-12, and 15-18 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Butler et al.* (U.S. Patent No. 6,589,726) in view of *Lefkowitz et al.* (U.S. Patent No. 6,258,454).

Specifically, the Office States as follows:

> Butler et al reference teaches a solid support array with hydrophilic sites that are spatially segregated by hydrophobic sites (i.e. intervening areas), wherein the hydrophilic sites contain free amino groups (i.e. surface modification) that can support non-covalent attachment to biological entitles including molecule (i.e. probe not forming a covalent bond and non-covalently attached to the substrate), and wherein solutions of reactants are added to hydrophilic sites using the drop-on-demand method that is analogous to the ink-jet printing technology (i.e. depositing solutions onto discrete sites), wherein the reactions on the support can be protein-protein interactions (i.e. probe is a protein). See column 6, lines 11-35; column 10, lines 40-57; column 12, lines 52-53; and column 14, line 4.

Office Action at 3. Applicant respectfully traverses. There are several deficiencies of *Butler* with respect to rendering independent claims 1 and 11 obvious, other than the ones admitted by the Office as follows:

> However, Butler et al fail to teach that the surface modification layer comprises at least a first moiety having the structure – Si-R^1 and a second moiety having the structure –Si-L-R^2, and wherein R^1 is a chemically inert moiety selected from the

group consisting of C3 to C30 alkyl and benzyl optionally substituted with 1 to 5 halogen atoms, L is a linking group, R2 is a hydrophilic moiety.

Office Action at 3-4. The deficiencies noted above are not remedied by combining *Butler* with *Lefkowitz*.

First, although *Butler* very generally describes that its solid supports can be employed as platforms for "protein-protein" interaction studies, *Butler* does not teach or suggest at least the following: "b) providing at least two solutions, each solution comprising a probe protein, and c) depositing the solutions provided in step b) onto discrete sites on the substrate, each solution being deposited onto its own discrete site, said depositing resulting in each probe protein not forming a covalent bond with R^2, but wherein each probe protein becomes non-covalently attached to the R^2 hydrophilic moiety on the substrate...." as recited in claim 1 (emphasis added). *Butler* does not teach or fairly suggest the probe proteins being provided in separate solutions and depositing the solutions on discrete sites on the substrate. Nor does *Butler* teach or suggest non-covalently attaching each probe protein to the R^2 hydrophilic moiety on the substrate. One skilled in the art upon reading *Butler* and *Lefkowitz* would not be motivated to (1) combine them, and (2) even if combined, reach all the steps recited in claim 1. Indeed, the term "protein" appears no where in *Lefkowitz*. Similarly, claim 11 also recites "wherein each probe protein is non-covalently attached to the R^2 hydrophilic moiety on the substrate" (emphasis added), which is not taught or suggested by the combined references. Therefore, claims 1 and 11 are allowable for at least this reason alone.

Second, the combination of the references fails to teach or suggest "the surface modification layer comprising at least a first moiety ... and a second moiety ..., wherein R^1 is a chemically inert moiety ... R^2 is a hydrophilic moiety," as recited in both independent claims 1 and 11. Instead, *Butler* discloses arrays that are "patterned with hydrophilic and hydrophobic sites." *Butler* at col. 6, lines 12-13. For example, *Butler* discloses "the density of derivatized, hydrophilic or in situ synthesis sites on an array...," (col. 4, lines 23-25) (emphasis added), "derivatizing a solid support to form hydrophilic or hydrophobic sites," (col. 4, lines 64-65), and that "[t]he area of each site may be about 0.1 $x10^{-5}$ to 0.1cm^2." In addition, *Butler* at col. 5, lines 64-65 and col. 6, lines 7-8 discloses "the total number of derivatized sites on an array is between about 10-500,000" and "the total number of in situ synthesis sites on an array is between about

10-500,000," which indicates that they derivatized hydrophobic and hydrophilic sites are the same size and density as the in situ synthesis sites. The present claims, however, recite a surface substrate that has been modified in bulk, not in discrete sites. Although at the atomic scale, the hydrophilic and hydrophobic moieties are distinct, at the 100 nm scale of synthesis, for example, the entire surface of the substrate has been modified to a certain degree of hydrophilicity. The probe proteins are deposited onto the arrays of claims 1 and 11 onto discrete sites on the substrate, and the size of the probe protein sites will be determined, at least in part, to the hydrophilicity of the substrate surface. Thus, the probe proteins, although deposited to form discrete sites on the substrate, are not deposited on specific hydrophobic or hydrophilic sites, but rather the substrate in general. *Lefkowitz* also fails to teach or suggest these features/steps. For at least this reason also, independent claims 1 and 11 are not taught or suggested by the combination of cited references and Applicant respectfully requests that the rejection be withdrawn.

Third, not only does *Butler* fail to teach fail to teach the surface modification layer comprises at least two moieties of the type described in claims 1 and 11, *Butler* also fails to teach or even suggest a surface modification at all that is non-covalently attached to a protein probe, or even any biomolecule. Instead, *Butler* discloses the following two options for attaching biomolecules, or "biological entities" to its surface tension arrays: (1) "hydrophilic sites may then by covalently couples with a linker moiety (*e.g.*, polylysine, HEG, PEG, etc.) capable of supporting chemical and biological synthesis"; and (2) "[t]he hydrophilic sites may also support non-covalent attachment to chemical or biological entities." *Butler* at col. 6, lines 28-32. Thus, not only does *Butler* fail to teach or suggest the silane moieties recited in claims 1 and 11, *Butler* also fails to teach or suggest a surface modification layer bound to the solid support, wherein each probe protein becomes non-covalently attached to the R^2 hydrophilic moiety on the substrate. The combination of *Lefkowitz* with *Butler* fails to remedy this deficiency, because *Lefkowitz* also does not teach or suggest a surface modification layer bound to the solid support, wherein each probe protein becomes non-covalently attached to the R^2 hydrophilic moiety on the substrate, as recited in claims 1 and 11. Therefore, for at least this reason also, claims 1 and 11 are not obvious in view of the combined cited references.

For at least each of these reasons, claims 1 and 11 are allowable over *Butler* in view of *Lefkowitz*. Applicant therefore respectfully requests that the rejection of claims 1 and 11 be withdrawn.

If independent claims 1 and 11 are allowable over the prior art of record, then their respective dependent claims 7-10, 12, and 15-18 are also allowable as a matter of law, because these dependent claims contain all features/elements/steps of their respective independent claims 1 and 11. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing reasons for the allowability of claims 1 and 11, these dependent claims recite further features/steps and/or combinations of features/steps (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable. By way of example, claim 7 recites "wherein at least one solution provided in step b) comprises a probe protein that is different from at least one other probe protein in another solution provided in step b)." As noted previously, neither *Butler* nor *Lefkowitz* teach or suggest providing at least two solutions of two proteins and depositing the solutions on the recited bioarray, much less two different proteins in the two solutions. Therefore, for at least this additional reason, claim 7 is allowable.

(b) Claims 2-6 and 13 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Butler* in view of *Lefkowitz* as applied to claim 1 above, and further in view of *Haab et al.* (Genome Biology, 2001)

Specifically the Office Action states as follows:

> Butler et al and Lefkowitz et al references have been disclosed above, but fail to teach the step of further drying the substrate after depositing the solutions.
>
> Haab et al reference teaches the step of drying glass microscope slides for 1 hour at 80 °C in a vacuum oven, in order to produce antibody/antigen immobilized slides. See page 12, left column 3rd paragraph.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Butler et al and Lefkowitz et al. with the step of drying glass microscope slides for 1 hour at 80 °C in a vacuum oven, as taught by Haab et al, in order to produce antibody/antigen immobilized slides. One of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of drying slides immobilized with antibodies or antigen, as taught by Haab et al, in the method proteins immobilized

> on glass slides, and the antibody of Haab et al is one type of protein that is also immobilized on glass slides.
>
> With regards to claims 3-6 and 13, Haab et al teach a blocking solution of 3% non-fat milk/PBS/0.02% sodium azide. See page 12, right column, 1st paragraph. In addition, with respect to claim 4, since blocking solution is placed on the entire slide, the hydrophobic sites (i.e. intervening areas) are subjected to non-covalent binding.

Office Action at 5-6. Applicant respectfully traverses. Dependent claims 2-6 and 13 are allowable for at least the same reasons as their respective independent claims 1 and 11. Additionally and notwithstanding the foregoing reasons for the allowability of claims 1 and 11, these dependent claims recite further features/steps and/or combinations of features/steps (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable. By way of example, claim 4 recites "the blocking protein becomes non-covalently attached to the substrate at the intervening areas and at the discrete sites." *Butler* in combination with *Lefkowitz* and *Haab* do not teach or suggest this feature. Therefore, for at least this additional reason, claim 4 is allowable.

(c) Claim 14 is rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over *Butler et al* in view of *Lefkowitiz et al.* as applied to claim 11 above, and further in view of *Silzel et al.* (Clin. Chem., 1998)

> Specifically, the Office Action states as follows:
>
> Butler et al and Lefkowitz et al references have been disclosed above, but fail to teach that each discrete site is in the range from 30 to 150 micrometers in diameter.
>
> Silzel et al reference teaches jet-printed spots of antibody reagent having diameters of 100 μm, in order to reduce the size of binding assays for reduced costs, faster chemistry, and equivalent or improved sensitivity. See page 2036, left column, 2nd paragraph; and page 2043, left column, last paragraph.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the apparatus of Butler et al and Lefkowitz et al with jet-printed spots of antibody reagent having diameters of 100 μm, as taught by Silzel et al, in order to reduce the size to reduce the size of biding assays for reduced costs, faster chemistry, and equivalent or improved sensitivity. One of ordinary

> skill in the art at the time of the invention would have had reasonable expectation of success in including spots of antibody reagent having diameters of 100 μm, as taught by Silzel et al, in the apparatus of Butler et al and Lefkowitz et al, since Lefkowitz et al teach molecule deposition by jet-printing techniques, and the antibody of Silzel et al is one type of molecule that can be deposited by jet-printing techniques.

Office Action at 6-7. Applicant respectfully traverses. Dependent claim 14 is allowable for at least the same reasons as claims 11 from which it depends. Additionally and notwithstanding the foregoing reasons for the allowability of claim 11, it recites further features that are patentably distinct from the prior art of record. Hence, there are other reasons why claim 14 is allowable. By way of example, claim 14 recites "wherein each discrete site is in the range from 30 to 150 micrometers in diameter." *Butler* in combination with *Lefkowitz* and *Silzel* do not teach or suggest this feature. Although *Silzel* discloses sites in a range of 100-200 μm in diameter, this range is not the range recited in claim 14. Applicant has been able to form discrete sites of a much smaller diameter than that disclosed in *Silzel*, thereby saving space on the array surface, if desired. Therefore, for at least this additional reason, claim 14 is allowable.

Newly Added Claims

Claims 19-20 have been newly added to further define and/or clarify the scope of the claims. No new matter has been added by the additional claims, and therefore a new search is not required to examine the newly added claims. Support for new claim 19 can be found at least in the specification on page 16, first full paragraph. The features recited in claim 19 have clear written support in, and are clearly enabled by, the specification. Further, claim 19 is allowable for at least the reason that it depends from independent claim 1. For at least this and other reasons, Applicant respectfully requests that newly added claim 19 be allowed.

Support for new claim 20 can be found at least on page 16, first full paragraph. The features recited in claim 20 have clear written support in, and are clearly enabled by, the specification. In addition, claim 20 is allowable over the prior art for at least the following reasons.

Butler describes a very complicated, multi-step procedure for forming hydrophobic and hydrophilic sites on its array substrate. Specifically, *Butler* recites the following two examples of its array fabrication process:

> In the present method of array fabrication, [1] the solid support may be first reacted with a suitable derivatizing reagent to form a hydrophobic surface. For example, the hydrophobic surface may be derivatized by vapor or liquid treatment of fluoroalkylsiloxane or alkylsilane. [2] The hydrophobic surface may then be coated with a photoresist substance, [3] photopatterned and [4] developed. [5] The exposed hydrophobic surface may be reacted with suitable derivatizing reagents to form hydrophilic sites. For example, the exposed hydrophobic surface may be removed by wet or dry etch such as oxygen plasma and then derivatized by aminoalkylsilane or hydroxylalkylsilane treatment to form hydrophilic sites. [6] The photoresist coat may be removed to expose the underlying hydrophobic sites. ...
>
> Alternatively, the solid support may be first reacted with a suitable derivatizing reagent to form a hydrophilic surface. For example, the hydrophilic surface may be derivatized by vapor or liquid treatment of aminoalkylsilane or hydroxylalkylsilane. The derivatized surface may then be coated with a photoresist substance, photopatterned, and developed. The exposed surface may be reacted with suitable derivatizing reagents to form hydrophobic sites.

Butler at col. 7, lines 47-60 and col. 8, lines 1-7 (emphasis and numerals added). As can be seen by the inserted numbers above, there are at least six steps in its process, which also requires the use of photoresists, a light source, *etc.*, all of which increases the cost, time, and space needed to fabricate *Butler*'s microarrays. In contrast, the method of claim 20 forms the functionalized substrate in one step, namely that recited in step a). The first silane is the derivatizing agent that reduces surface energy as desired, while the second silane provides the surface functionalization necessary for covalent attachment of an additional molecular moiety.

Moreover, it would not been obvious to combine the teachings of *Butler* with those of *Lefkowitz* to achieve the method of claim 20. Instead *Butler* teaches away from step a) of claim 1. Specifically, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant...." *In re Gurley*, 2 F.3d 551, 31 USPQ2d 1130, 1131 (Fed Cir. 1994) (emphasis added). *Butler* praises its method of fabricating an array, and touts its advantages at the following passage:

> The advantages of the instant methods are (1) the photoresist acts as a physical barrier separating the hydrophilic and hydrophobic derivatization processes and inhibits any cross derivatization between the two processes and (2) there is no photoresist residue present on the array surface prior to derivatization. By using the instant array fabrication methods, the undesirable coupling between photoresist and derivatizing reagent is minimized and the resulting solid support is more uniform with respect to derivatization, in situ synthesis, and array applications. This method thus allows more control of photopatterning, eliminates batch to batch variability, and increases the step yields of in situ synthesis.

Butler at col. 8, lines 17-29. By listing the advantages in its method, *Butler* teaches away from looking for further solutions in other areas of the art. At the very least, combining *Butler* with *Lefkowitz* results in an unwarranted modification of *Butler*. "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 U.S.P.Q.2d 1780 (Fed Cir. 1992). Nothing in *Butler* suggests the desirability of modifying its method of fabricating an array to result in the method recited in claim 1, or even that deficiencies in its methods that could be solved by looking to the teachings of *Lefkowitz*. Therefore, for at least this reason also, claim 20 is not obvious in view of the combined cited references.

CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicant respectfully submits that all rejections have been traversed, and/or accommodated, and that the now pending claims 1-20 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE

I hereby certify that this correspondence (19 pages) is being faxed to (571) 273-8300; Attn: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on September 26, 2005

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The following is a list of documents enclosed:

Return Postcard
Request for Continued Examination (RCE)
Request for 1-Month Extension of Time
Amendment Transmittal Page
Response (With Amendments)

Further, the Commissioner is authorized to charge Deposit Account No. 50-1078for any additional fees required. The Commissioner is requested to credit any excess fee paid to Deposit Account No. 50-1078.